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MAGNETIC RESONANCE

Structural brain alterations of Down's syndrome in early childhood evaluation by DTI and volumetric analyses

Hediye Pınar Gunbey[1] · Meltem Ceyhan Bilgici[1] · Kerim Aslan[1] · Arzu Ceylan Has[2] · Methiye Gonul Ogur[3] · Aslıhan Alhan[4] · Lutfi Incesu[1]

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Abstract

Objectives To provide an initial assessment of white matter (WM) integrity with diffusion tensor imaging (DTI) and the accompanying volumetric changes in WM and grey matter (GM) through volumetric analyses of young children with Down's syndrome (DS).

Methods Ten children with DS and eight healthy control subjects were included in the study. Tract-based spatial statistics (TBSS) were used in the DTI study for whole-brain voxelwise analysis of fractional anisotropy (FA) and mean diffusivity (MD) of WM. Volumetric analyses were performed with an automated segmentation method to obtain regional measurements of cortical volumes.

Results Children with DS showed significantly reduced FA in association tracts of the fronto-temporo-occipital regions as well as the corpus callosum (CC) and anterior limb of the internal capsule ($p < 0.05$). Volumetric reductions included total cortical GM, cerebellar GM and WM volume, basal ganglia, thalamus, brainstem and CC in DS compared with controls ($p < 0.05$).

Conclusion These preliminary results suggest that DTI and volumetric analyses may reflect the earliest complementary changes of the neurodevelopmental delay in children with DS and can serve as surrogate biomarkers of the specific elements of WM and GM integrity for cognitive development.

Key Points

- *DS is the most common genetic cause of intellectual disability.*
- *WM and GM structural alterations represent the neurological features of DS.*
- *DTI may identify the earliest aging process changes.*
- *DTI-volumetric analyses can serve as surrogate biomarkers of neurodevelopment in DS.*

Keywords Down's syndrome · Brain · MRI · DTI · Volumetry

Introduction

Down's syndrome (DS), or trisomy 21, is the most common genetic cause of intellectual disability and occurs in 14.7 out of every 10,000 live births [1]. The association of several neurological features, such as impairments in language [2], cognition [3], learning and memory [4], with unclear origin make it one of the most speculated neurodevelopmental disorders in childhood. The cognitive profiles of DS include language deficits in articulation [5], syntactic weakness [6] and significant verbal short-term memory deficits [7] accompanied by motor weaknesses [8].

Although the clinical features of DS have been characterized, few neuroimaging studies have qualified the pathophysiology of the neurological deficits in DS. As the first manifestation of neuroanatomical abnormality, a characteristic reduced brain size of children with DS appears in the 4- to 5-month fetus and progresses during the last 3 months of gestation [9, 10]. Structural MRI reports, based on fewer than 15 original studies in children and youths, have suggested that the total

✉ Hediye Pınar Gunbey
hpgunbey@hotmail.com

[1] Faculty of Medicine, Department of Radiology, Ondokuz Mayıs University, Neuroradiology Section, 55139 Kurupelit, Samsun, Turkey

[2] National Magnetic Resonance Research Center, Bilkent University, Ankara, Turkey

[3] Department of Genetics, Ondokuz Mayıs University, Samsun, Turkey

[4] Department of Statistics, Ufuk University, Ankara, Turkey

brain volume is smaller [11–14], with specific reductions in cerebellar [11–13, 15] and hippocampal volumes [12, 14, 15]. Additionally, several studies have reported regional reductions in the frontal and temporal lobes [13, 14] and preserved parietal lobar grey matter (GM) volume [12] in children. Knowledge of GM involvement has been extended by recent paediatric voxel-based morphometry (VBM) studies with high spatial resolutions. Differences in GM density have been reported in the frontal temporal lobes and cerebellum [15–17]. The latest study utilizing cortical morphometry in young people also noted reductions of cortical GM and white matter (WM) volumes, accompanied by decreased frontotemporal surface areas [18]. A case study of cortical morphometry using FreeSurfer reported reduced volumes of bilateral precentral and cingulate gyri [19]. FreeSurfer is a powerful tool with high reproducibility and accuracy for extensive and automated analysis of the human brain [20]; it provides completely automated parcellation of the cerebral cortex and subcortical structures.

Due to the severity of the DS cognitive phenotypes, it is surprising that no existing study has evaluated the WM integrity of children with DS. The impaired intellectual function in DS is caused by abnormalities in memory, language and learning [21]. Morphosyntax, verbal short-term memory and explicit long-term memory are typically affected by memory and language abilities. Along with volume reductions, the connections of white matter structures between the frontal and temporal lobes may also be affected and may disclose the underlying pathophysiology of these deficits. In addition, emotion and the affected visuospatial functions may also be linked to limbic and temporo-occipital connections. Lastly, an evaluation of cerebellar microstructures may define the involvement of motor and non-motor functions in the cerebellums of patients with DS [22]. Due to the growing interest in potential alterations in anatomical connectivity, diffusion tensor imaging (DTI) has become a popular tool for assessing structural connectivity in the human brain.

DTI is a non-invasive, advanced MRI method that characterises the microstructure of WM in vivo by quantitatively measuring the diffusion of water [23]. DTI parameters, especially fractional anisotropy (FA), identify the directional diffusion properties of tissues and are sensitive to anomalies in axonal density, diameter and myelination within WM tracts [24]. Another DTI parameter, mean diffusivity (MD), reflects the magnitude of diffusion that is independent from anisotropy and demonstrates the degrees of myelination, interstitial space and axonal density. According to the existing literature, only one DTI study has evaluated the WM integrity of DS in adults: Powell et al. [25] reported FA decline in evaluating dementia in DS adults. Against the background of morphological brain changes that have been detected as early as in 4- to 5-month fetuses, we aimed to investigate 2- to 4-year-old children with DS. These data provide an initial assessment of WM integrity and accompanying white and grey matter volumetric changes in early DS childhood.

Materials and methods

Subjects

The study included ten children with DS (five girls and five boys; mean age 2.6 ± 0.69 years) and eight healthy controls (four girls and four boys; mean age 2.5 ± 0.707 years). The patients were recruited from DS individuals who were referred for brain MRI acquisition by the Department of Genetics during clinical follow-up. The diagnosis of DS was confirmed by karyotype examinations that showed trisomy of the chromosome 21. Exclusion criteria included untreated medical conditions that might affect cognition (e.g. hypothyroidism in DS). The control group consisted of eight right-handed, age- and sex-matched healthy subjects who had been referred for MRI scan for other reasons and had normal findings on structural MRI. Controls were excluded for having any history of previous neurological, psychiatric or systemic disease. After a complete description of the study, informed consent was obtained from the patients' parents before the administration of sedative drugs prior to going for the MR scan. The study was approved by the Ethics Committee of Ondokuz Mayıs University Medical School, Samsun, Turkey.

The MRI studies were conducted under sedation with chloral hydrate (CH). The protocol for paediatric MRI sedation was 50 mg/kg CH, followed by a second dose if sedation failed. In patients who were monitored, oxygen saturation and electrocardiogram monitoring were applied during sedation. The patients were discharged 1–2 hours after they recovered.

Image acquisition and processing

All images were acquired on a 1.5-T Philips Gyroscan Intera system equipped with a Synergy-L Sensitivity Encoding (SENSE) head coil. The DTI data were acquired using a 16-direction EPI sequence with 60 contiguous 2-mm AC-PC aligned interleaved slices with no gap (TR/ TE = 10.15/ 90 ms; matrix = 128 × 128; b-value = 1,000; FOV = 256 mm, 2-mm isotropic resolution, NSA = 3). In addition, a high resolution T1-weighted 3D gradient-echo sequence (TR/ TE = 7.2/33 ms; matrix = 256 × 256 pixels; NSA = 1; FOV = 256 mm; slice thickness = 1 mm; gap = 0 mm; flip angle = 8°) of structural images of 160 slices of the entire brain was acquired for anatomical reference.

DTI data were analysed using FSL v. 4.1.5 (Functional MRI of the Brain software library, FMRIB). Preprocessing of the raw images of diffusion-weighted data involved correcting of head motion, eddy current distortion and diffusion tensor fitting using FMRIB's Diffusion Toolbox (FDT v. 2.0). After pre-processing, FA and MD were calculated. Tract-based spatial statistics (TBSS) (TBSS v. 1.2; http://www.fmrib.ox.ac.uk/fsl/ tbss/) were used for voxelwise statistical analyses of the DTI data. The thinned mean FA skeleton

was computed after registration of FA maps and aligning to the average space as input for TBSS. A permutation-based, non-parametric test was performed with 500 permutations to produce the voxelwise statistics.

The threshold-free cluster enhancement was used to avoid the use of an arbitrary threshold in the initial cluster formation and output was corrected for multiple comparisons. Family-wise error corrected maps were obtained with p-values less than 0.05. Standard cluster-based thresholding corrected for multiple comparisons, comprising Gaussian-smoothing, thresholding of the smoothed data at a cluster-forming t threshold of two and, finally, formation of the contiguous clusters of supra-threshold voxels (using 26-neighbour connectivity) were carried out. Supratentorial WM clusters with significant changes on the resulting TBSS maps were extracted as regions of interest (ROIs) and registered and overlaid onto an anatomical Montreal Neurological Institute (MNI) template. These ROIs were labelled according to Johns Hopkins University WM tractography and the International Consortium for Brain Mapping DTI-81 WM atlases in FSL, and the mean diffusion indices of the ROIs were calculated. The author who performed the measurements was blind to subjects' clinical information and compared right and left sides. For the special analyses for measuring FA values, ROIs were drawn to the right cerebral peduncle (R-CP), bilateral posterior limb of internal capsule (PLIC), uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), cingulum (CIN) and corpus callosum minor forceps (CCminF) (Fig. 1).

The volumetric segmentation analysis was performed using Freesurfer v. 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) including the removal of non-brain tissue (skull, eyeballs and skin), using an automated algorithm with the ability to successfully segment the whole brain without any user intervention. Next, cortical surface reconstruction methods were applied to acquire regional measurements of cortical volume (mm^3). Fischl et al. [26] described the automated procedures for volumetric measurements of the different structures of the brain. After checking the reconstructed cortical surface models to confirm segmentation accuracy for each participant, regions with poor segmentation accuracy were excluded from analyses due to poor image quality or misregistration. Cortical surfaces were automatically parcellated and combined to create averages for cortical-total GM and for frontal, temporal, parietal and occipital lobar regions.

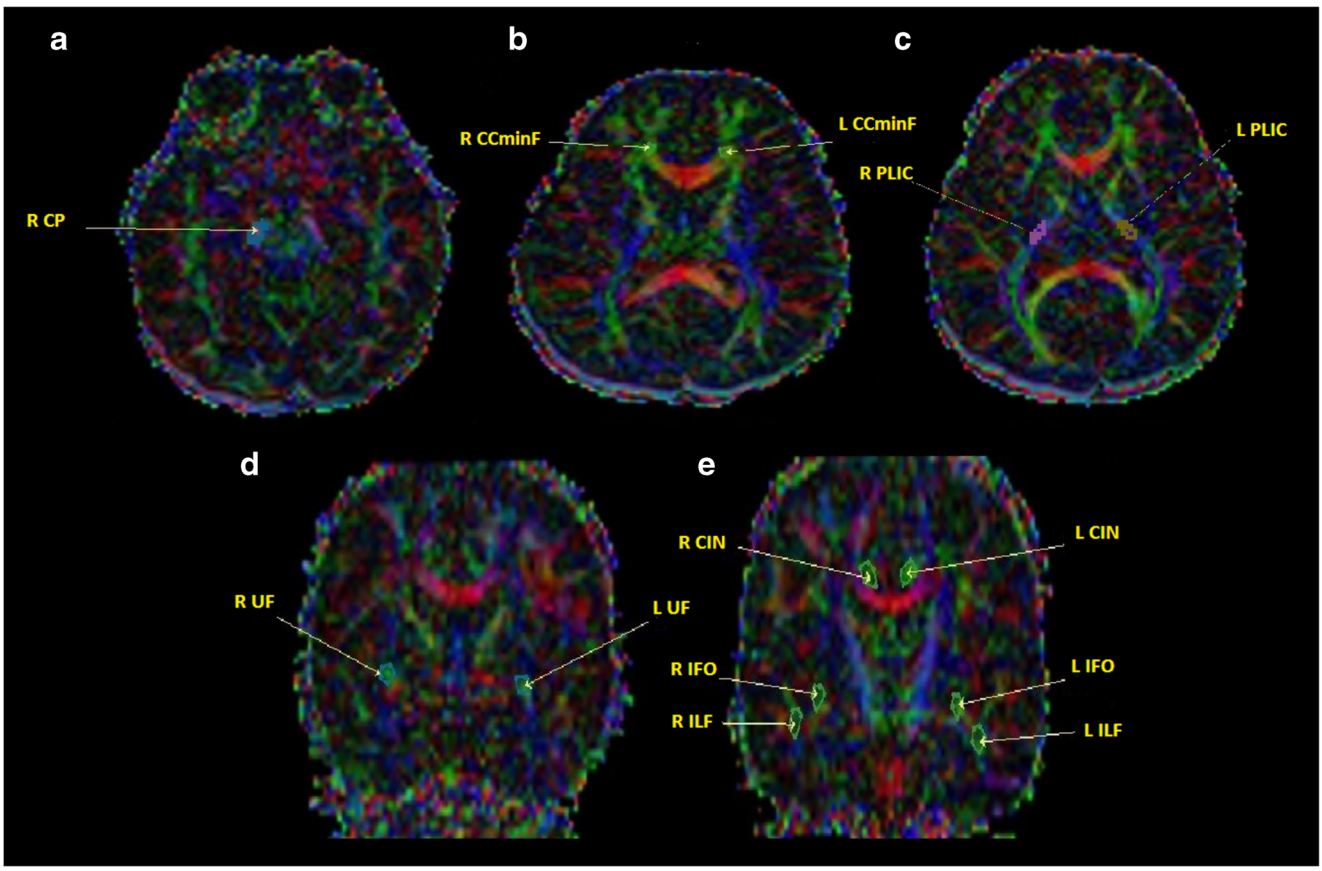

Fig. 1 The regions of interest (ROIs) on coloured fractional anisotropy (FA) maps on axial (A, B, C) and coronal sections (D, E). *R* right, *L* left, *CP* cerebral peduncle, *PLIC* posterior limb of internal capsule, *IFOF* inferior frontooccipital fasciculus, *ILF* inferior longitudinal fasciculus, *UF* uncinate fasciculus, *CIN* cingulum, *CCminF* corpus callosum minor forceps

The Shapiro-Wilk test was used to determine normality, and the Mann-Whitney U test was used for comparisons of the means of variables with controls. Correlations between volumetric values and volumetric-DTI values were calculated with Spearman's correlation test. A p-value less than 0.05 was considered to indicate statistical significance.

Results

Volumetric analyses

Children with DS showed significant reductions in the regional GM volume of of the left putamen, bilateral thalamus proper, caudate nucleus and cerebellar cortex, as well as the brain stem and corpus callosum (CC) ($p < 0.05$). Additionally, subcortical GM volume (SGMV) and total cortical GM volume (TCGMV) of both hemispheres and right cerebellar WM volume were significantly lower in DS subjects compared to controls ($p < 0.05$) (Table 1). There were no significant differences in the total WM, total GM and brain segmentation volumes ($p > 0.05$) between DS subjects and the controls.

DTI analyses

The whole brain TBSS revealed extensive reductions of FA in the supratentorial WM including right-CP, right-UF, CC body, bilateral ILF/IFOF and right anterior limb of the internal capsule (ALIC). Clusters showing increments of MD values for DS compared to control subjects were found in the CP, ILF and IFOF of the right hemisphere and in the external capsule and posterior thalamic radiation (PTR) of the left hemisphere.

Table 1 Regional brain volumes of subjects with Down's syndrome versus control subjects

Region	Children with Down's syndrome (N = 10) mean ± SD	Control group (N = 8) mean ± SD	p-value
Volume measures (cm^3)			
Brain segmentation volume	860.2 ± 50.4	845.4 ± 44.4	0.624
R CGMV	219.2 ± 16.1	234.1 ± 18.1	0.037*
L CGMV	219.5 ± 9.2	233.7 ± 18.3	0.049*
T CGMV	438.6 ± 25.3	467.8 ± 37.1	0.037*
SC GMV	41.7 ± 2.5	45.6 ± 3.2	0.014*
T GMV	579.3 ± 42.3	563.2 ± 26.8	0.270
R WMV	125.8 ± 9.3	128.9 ± 10.8	0.462
L WMV	124.7 ± 9.3	128.4.6 ± 1.0	0.327
T WMV	250.5 ± 18.5	257.3.6 ± 20.7	0.327
R thalamus	5.0 ± 0.2	5.4 ± 0.2	0.014*
L thalamus	4.9 ± 0.1	5.3 ± 0.3	0.010*
R caudate	3.0 ± 0.1	3.3 ± 0.4	0.05*
L caudate	2.7 ± 0.4	3.2 ± 0.4	0.05*
R putamen	5.0 ± 0.7	4.3 ± 0.6	0.66
L putamen	4.5 ± 0.4	5.0 ± 0.6	0.05*
R pallidum	1.3 ± 0.1	1.4 ± 0.1	0.540
L pallidum	1.5 ± 0.09	1.7 ± 0.2	0.02*
R hippocampus	2.9 ± 0.2	2.8 ± 0.4	0.903
L hippocampus	2.9 ± 0.2	3.0 ± 0.2	0.391
R amygdala	1.0 ± 0.1	1.0 ± 0.1	0.270
L amygdala	1.0 ± 0.1	1.0 ± 0.1	0.806
Brain stem	10.6 ± 1.1	12.0 ± 1.3	0.027*
R cer cortex	5.4 ± 0.2	42.7 ± 1.3	0.002**
R cer WMV	5.6 ± 0.9	7.9 ± 0.9	0.007**
L cer cortex	33.2 ± 4.0	41.3 ± 0.8	0.002**
L cer WMV	7.7 ± 2.8	7.7 ± 1.0	0.713

R right, *L* left, *T* total, *GMV* grey matter volume, *CGMV* cortical grey matter volume, *SC* subcortical, *WMV* white matter volume

*Analysis of variance $p < 0.05$; **$p < 0.01$

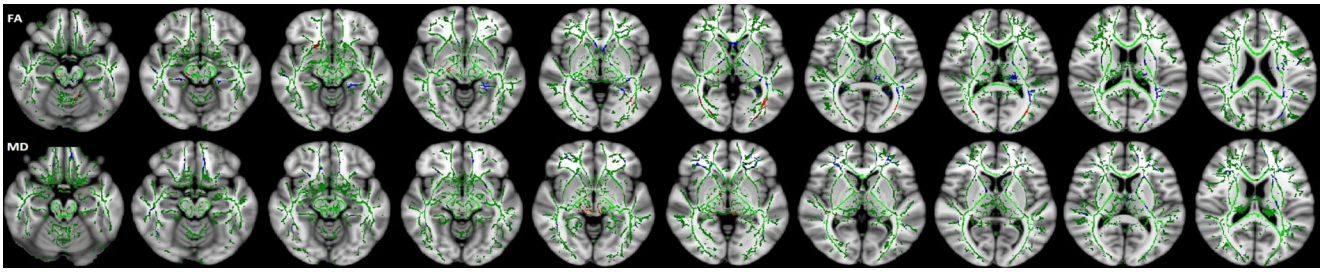

Fig. 2 Tract-based spatial statistics (TBSS) (family-wise error– corrected threshold-cluster extend voxel p maps) display clusters with significantly different fractional anisotropy (FA) and mean diffusivity (MD) of children with Down's syndrome (DS) compared to control participants at $P < 0$ .05. For all diffusion measures, blue shows increased values and red shows decreased values. FA skeleton projected on a mean FA map is shown in green

Clusters of ALIC and anterior parts of anterior thalamic radiation (ATR), UF, IFO and anterior corona radiate showed bilateral increments of MD. Notably, the clusters in the R-CP and bilateral IFO had lower FA values that were associated with greater MD (Fig. 2).

Interestingly, individuals with DS exhibited greater FA in several clusters, such as the left superior cerebellar peduncle, frontal part of left IFO, bilateral medial lemniscus, PLIC and stria terminalis, temporal part of bilateral cingulum, right optic tract and ILF.

Furthermore, significant FA differences were revealed by ROI analyses of the right CP ($p = 0.033$), right ILF ($p = 0.044$), left UF ($p = 0.006$) and right UF ($p = 0.016$) between the DS and control groups (Fig. 3). MNI coordinates of selected ROIs and significant FA values are summarized in Table 2.

In correlation analyses, while right-CIN showed a positive correlation with right-CP ($p = 0.004$, $r = 881$), left-CIN correlated with left-PLIC ($p = 0.047$, $r = 714$) in control subjects. In the DS group, positive correlations were seen between the right-CIN and right-CP ($p = 0.029$, $r = 685$), the right-UF and right-CP ($p = 0.024$, $r = 685$) and the right-ILF and left-IFOF ($p = 0.019$, $r = 721$). The left-UC correlated positively with the CCminF in both DS ($p = 0.004$, $r = 818$) and control subjects ($p = 0.037$, $r = 673$).

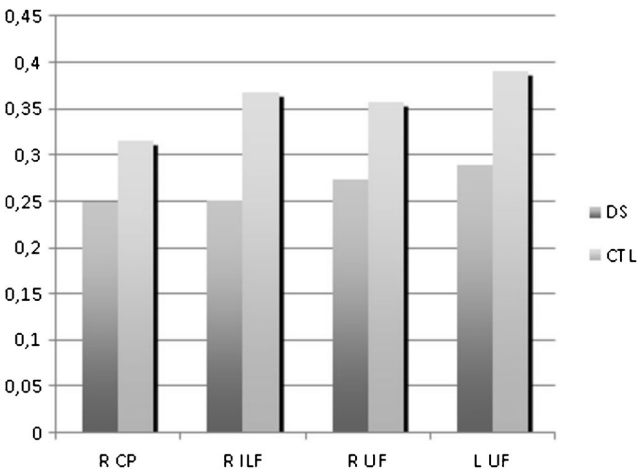

Fig. 3 Fractional anisotropy (FA) values of the most affected white matter (WM) tracts from region of interest (ROI) analyses between children with Down's syndrome (DS) and control subjects ($p < 0.05$). *R* right, *L* left, *CP* cerebral peduncle, *ILF* inferior longitudinal fasciculus, *UF* uncinate fasciculus

Combined volumetry and DTI results

The correlation analyses of volumetry and DTI values showed a positive ($p = 0.016$, $r = 733$) relationship between FA of the CCminF and the anterior volume of the CC, which was an expected result. The FA values of the right PLIC correlated positively with the right WM ($p = 0.006$, $r = 794$) and total WM volumes ($p = 0.005$, $r = 806$).

Discussion

The alterations in neuronal and cognitive development with premature aging requires clear understanding of the earliest changes in brain structures for the earliest treatment strategies for DS. Although DS is a neurodevelopmental disorder, most neuroimaging studies have investigated the volumetric analyses of adult and adolescent samples not fit into a narrow age range. Interestingly, no study has investigated the WM integrity of children with DS. The present study revealed preliminary data on alterations in GM and WM integrity through volumetric and DTI analyses in a homogeneous sample of participants between 2 and 4 years old, which is a critical age range for brain overgrowth.

Volumetry

Results of the present study documented lower widespread GM volumes of SGMV and TCGMV consistent with two recent studies that focused on cortical morphometry in young DS subjects [18, 27]. A reduced cortical GM volume may reflect the post-mortem findings of simplified gyral patterns, decreased neuronal density, lamination [28] and reduction of about 30–40 % in the number of both neurons and glial cells

Table 2 Montreal Neurological Institute (MNI) coordinates of selected regions of interest (ROIs) and significant fractional anisotropy (FA) values of both Down's syndrome subjects and controls

ROI	MNI coordinates (x,y,z)	Down's syndrome FA	Control group FA	p-value
R CP	21, − 43 , − 36	0, 2482049	0,314408125	0.033
R PLIC	24, − 18, 13	0, 4677318	0,38414875	0,091
L PLIC	− 23, − 18, 13	0, 4924511	0,387061375	0,062
R IFOF	35, − 10, − 12	0, 3989686	0,479078625	0,131
L IFOF	− 36, − 14, − 12	0, 4367896	0,48864925	0,424
R ILF	42, − 29, − 12	0, 3679816	0,250141	0.044
L ILF	− 41, − 29, − 12	0, 2487341	0,24346275	0,051
R UF	36, 2, − 15	0, 2727017	0,3578645	0.016
L UF	− 35, − 5, − 15	0, 390128	0,289574875	0.006
R CIN	8, 19, 29	0, 3126787	0,2359035	0,214
L CIN	− 7, 13, 29	0, 2818979	0,200515375	0,183
R CC minF	− 7, 30, 5	0, 5488533	0,40169375	0,155
L CC minF	9, 29, 5	0,5390404	0,380602625	0,131

R right, *L* left, *ROI* region of interest, *MNI* Montreal Neurological Institute, *CP* cerebral peduncle, *PLIC* posterior limb of internal capsule, *IFOF* inferior fronto-occipital fasciculus, *ILF* inferior longitudinal fasciculus, *UF* uncinate fasciculus, *CIN* cingulum, *CCminF* corpus callosum minor forceps, *FA* fractional anisotrophy

of neocortical regions in DS [29]. This abnormal development of cortical neurons can lead to learning and memory problems or seizures that begin to emerge in late infancy.

Although a regional GM volume decline in the left putamen, bilateral thalamus and caudate nucleus as well as the brain stem represents initial data in volumetric neuroimaging studies of DS, Anderson et al. [30] reported involvement of these structures with functional MR imaging (fmri) and Karlsen et al. [29] showed there were about 40 % fewer neurons in the thalami of DS brains compared to control brains. Gating sensory input from the brainstem and sensory areas to the cortex and other subcortical regions leads the thalamus and basal ganglia to act as key components for integrating cognition and affective experience. Therefore, these structural alterations may be considered in causative issues of cognitive impairment in DS.

The significantly smaller CC was consistent with previous findings [31], and reflects the loss of neocortical neuronal projections involved in the maintenance of higher cognitive processes. Our findings of smaller cerebellar volumes were also consistent with the results of prior neuroimaging studies in children with DS [12, 13, 32]. In terms of cortical and WM volume reductions, the results of the current study are concordant with two recent paediatric neuroimaging studies utilizing voxel-based morphometry [15, 17]. The cerebellum plays a major role in the regulation of proprioceptive motor control and motor learning as verified by the research of Rigoldi et al. [16], reporting a strong relationship between cerebellar vermis volume reduction and quality of gait in patients with DS. The involvement of the cerebellum might contribute to the cognitive phenotypes of DS through the non-motor cortico-cerebellar and cerebellar-limbic circuits that are involved in emotion, attention, working memory, executive control and language learning [33]. Recently, Menghini et al. [17] found significant regional reductions in GM and positive correlations between GM density of cerebellum and measurements of linguistic ability.

Our results did not show as significant a difference in terms of total brain, segmentation and hippocampal volumes as previous reports [12, 14, 15]. The total and subcortical GM volume reduction may not have a significant influence on total brain and hippocampal volume in this age group. A comparison with these studies is challenging due to the wide age range in their included participants.

While we examined the youngest population of DS in neuroimaging studies, they also included young adults, with difficulties in establishing findings on early developmental or neurodegenerative progress.

DTI

These DTI data represent the first published study of children with DS. We observed significantly lower FA values in a subset of supratentorial WM tracts, which included the right-CP, right-UF, CC body, right ALIC and bilateral ILF and IFOF in DS. Our TBSS study's results were consistent with those of Powell et al.'s DTI study on the frontal WM integrity of adults with DS [25]. As they reported we also detected much of the FA decrease in frontal circuits.

The internal capsule comprises much of the centrum semiovale and courses from the cortex to the brainstem continuing as cerebral peduncles. Its first subdivision ALIC connects the thalamus and prefrontal cortex and contains axons in the frontopontine pathway. ALIC involvement in several

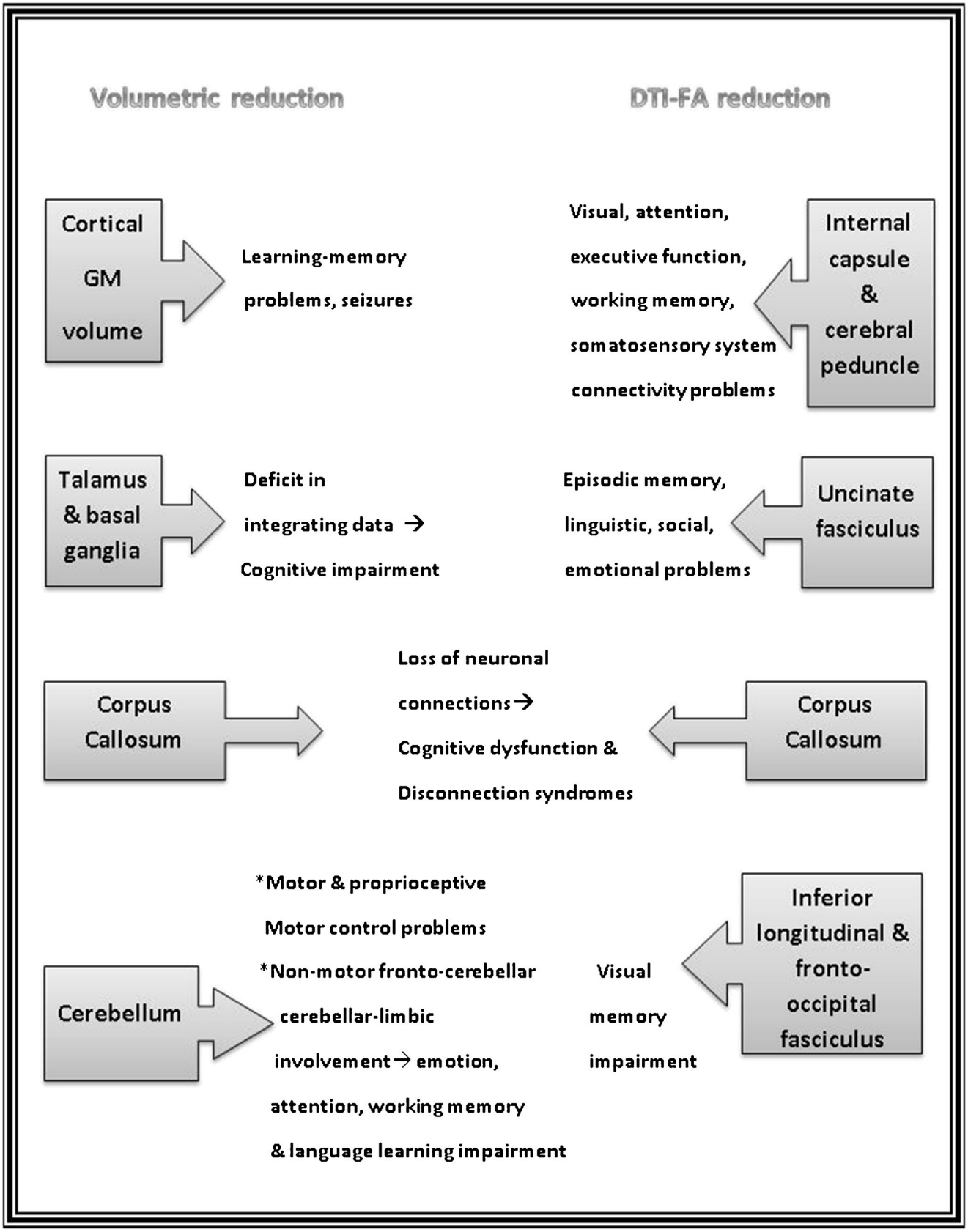

Fig. 4 Summary of the most affected regions through volumetric and diffusion tensor imaging (DTI) analyses in the present study and the possible outcomes of these results

diseases such as schizophrenia, autism and the evidence of neuropsychological abnormalities including memory impairment due to damage in genu and ALIC have been reported before [34–36]. Therefore, our findings on WM degradation in the ALIC may indicate the reduced function of the prefrontal cortex for executive function and spatial working memory in patients with DS. The impairment of thalamocortical fibres in the ALIC may affect the crucial connectivity of visual, attentional and somatosensory systems in patients with DS [37].

Another important aspect of frontal circuits is involvement of the UF which is one of the major long-range WM tracts that connects the orbitofrontal cortex to the anterior temporal lobes. It is assumed that the functions should align associative and episodic memory, linguistic and social-emotional functions due to typically relating with the limbic system. Deficits of short-term and episodic memory tasks and reductions in fMRI signals on the medial temporal lobe may be related to damage to the UF [38–40]. The FA decrease in UF may represent an earlier stage of hippocampal damage and reflect the affected cellular integrity with functional deficits.

Many individuals with DS face the daily challenge of negatively affected visual object memory [41]. The ILF is a ventral associative bundle with considerable functions in visual perception and object recognition. It connects the occipital lobe to the anterior part of the temporal lobe that runs above the optic pathways and overlaps with the IFOF, which is another direct pathway that connects the occipital, orbito-frontal and posterior-temporal areas. On the other hand, the ILF is linked to the UF so that it can transfer information to the orbitofrontal brain. In our study, degradation of integrity of the ILF and IFOF with decreased FA values may indicate visual memory impairment consistent with Ortibus et al. [42], who have reported a relationship between ILF and IFOF integrity in children with visual- perceptual impairment [42].

Finally, decreased FA in the CC, the largest WM structure that facilitates interhemispheric communication, provides significant evidence of WM involvement in DS. Lower FA values are consistent with the recent DTI study in adults by Powell et al. [25] and showed a positive correlation with decreased volumetry in our study. Cognitive dysfunction and several disconnection syndromes may result from the impaired integrity of the CC. The positive relationship between the UF and CCminF may indeed reflect functional similarity as well as spatially sharing overlapping paths.

MD and FA are complementary measurements of tissue damage. In our study, the UF, ILF, IFO, right-CP and ALIC showed decrements in FA accompanied by increments in MD, presenting the major affected fibres of WM in DS. However, independent MD increments in the clusters of the external capsule, anterior corona radiata and thalamic radiatio may demonstrate that diffusion is increased subjectively but the cellular integrity of these tissue is not significantly affected.

The FA increment is an uncommon finding during neurodegenerative processes. However, increased FA values have been reported in autism and attention-deficit/hyperactivity disorder [43, 44] before. Thus, we can infer that the initially defective myelinated nerve sheaths of children with DS can show excessive hyperplasia during the overgrowth phase of brain development and lead to a high FA value of WM, whereas this extreme myelination may not completely compensate the defective cognitive function of DS. As previously reported, this condition may also be related to brain compensatory mechanisms of synaptic plasticity [45–47], even if the function is not well preserved.

The most affected regions through volumetric and DTI analyses in the present study and the possible outcomes of these results are summarized in Fig. 4.

Limitations

The present study has some limitations in that the cognitive/motor functions of patients were not evaluated and the cross-sectional study method involved a small patient group using 1.5-T MRI.

Conclusion

The neurological deficits of DS appearing from childhood should be investigated for potential treatment strategies. To our knowledge, the preliminary results of WM alterations in children with DS in the present study may define impaired integrity of several fibres and may be related to executive function, visual and spatial memory, and disconnection syndromes. Additionally, as the first neuroimaging volumetric data in such a young patient group with DS, the results may suggest that cerebellar, CC, cortical, subcortical and deep GM volume reductions begin as early as 2 years of age. The lack of brain segmental volume reduction with more extensive WM impairment in this age group may suggest that WM degeneration may be an early step in neurodevelopmental delay. In future studies, combining DTI and functional MRI in larger patient groups will contribute to providing further details about tissue microstructure and function of DS in neurodevelopmental and neurodegenerative progress.

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